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10/574,645	08/10/2006	David Salomon	251206	9318

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

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11/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,645	SALOMON ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 7-26* is/are pending in the application.

4a) Of the above claim(s) *7-14 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/29/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 1, 15-20 and over expression of Cripto-1 in the reply filed on 9/24/2007 is acknowledged. The traversal is on the ground(s) that applicant asserts the special technical feature is detection of neurodegenerative disease and that claim 1 is a linking claim. This argument has been reviewed but is not found persuasive because all the claims require detecting of Cripto-1, which is not a special technical feature over the prior art. Further claim 1 of 3/29/2006 was not a linking claim, however the examiner concurs that amended claims 15-21 do in fact make claim 1 a linking claim. The response further argues that the examiner did not present arguments as to the independence and distinctness of the inventions, these arguments are spurious as this application is a 371 and lack of unity practices are used.

2. Claims 7-14 and 21-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/24/2007.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method of detecting neurodegenerative disease in a mammal comprising assaying the expression level of a Cripto-1 gene product in the central nervous system of the mammal wherein overexpression of the Cripto-1 gene product is indicative of neurodegenerative disease in the mammal.

The claims are thus broadly drawn to detecting any neurodegenerative disease based on the overexpression of Cripto-1 gene product. Claim 16 further limits the claims to s selected from the group consisting of NeuroAIDS, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and encephalitis.

The claims are thus broadly drawn to the detection of Cripto-1 mRNA or protein.

The claims are drawn detection in "any" mammal, although claim 15 draws the claim to humans. Thus the claims broadly encompass dog, cat mouse, whale, etc.

The claims are drawn to "any" Cripto-1 gene product. This broadly encompasses any splice variant, SNP, allele, mutant, etc.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches in example 2 a study of 5 pig tailed Macaque. The study compares the expression of RNA isolated from the parietal cortex of 1 control uninfected Macaque with expression from 4 macaque infected with SHIV (see paragraph 0073). The specification further teaches, "a more stringent 2.5 difference was chosen as an arbitrary cutoff value for differences in gene expression." (see paragraph 0073). The specification further teaches the relative expression was calculated by use of normalization spots and standard housekeeping genes.

The specification teaches in Table 2 there was a 9.56 fold increase in Tetracarcinoma-derived growth factor (Cripto-1) in the uninfected macaque relative to the 4 SHIV infected macaque.

The specification teaches, " the function of Cripto in neurons in the adult brain and its upregulation in the brains of SHIV-infected macaques are also unknown" (see paragraph 0086).

The specification further suggests in example 5, future studies to determine the Cripto-1 expression patterns in Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and encephalitis.

Presence and absence of working examples

The specification teaches a single study involving 4 SHIV infected macaque and 1 non-infected control in which Cripto-1 is upregulated. However, this study uses a single control that has not been infected with any virus. Further this study examines tissue that has been collected post-exsanguinations and thus altered expression may merely be differences in the handling of the one control sample.

The specification does not teach any working examples of diagnosis based on detection of overexpression of Cripto-1.

The specification does not teach any studies in humans.

The specification is silent to the house keeping gene used to normalize the expression data.

The state of prior art and the predictability or unpredictability of the art:

Vandesompele teaches, " Accurate normalization of gene expression levels is an

absolute prerequisite for reliable results, especially when the biological significance of subtle gene expression differences is studied" (see page 9, 2nd column, discussion) (Vandesompele et al (Genome Biology (2002) volume 3 , pages 1-11). Vandesompele teaches, " That the conventional use of a single gene normalization leads to relatively large errors in a significant portion of samples tested" (see abstract, results). Vandesompele teaches that ACTB (beta actin) appears to be the one of the worst genes fro normalization and thus resulting in large normalization errors (see page 10, 1st paragraph). Vandesompele teaches at least 3 housekeeping genes are required for accurate normalization (see page 10, 1st column, 1st full paragraph). Vandesompele thus teaches that studies of gene expression using a single gene for normalization are unpredictable due to the large variation in the expression of the genes used for normalization.

Because the claims encompass any level of increased gene expression, it is relevant to point out that the post-filing art of Cheung et al (Nature Genetics (2003), volume 33 pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene

expression is indicative of a phenotype.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology (2001) volume 195, pages 53-65). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion).

The prior art of Newton et al (Journal of computational biology (2001) volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed one of skill in the art would first have to determine if a predictive relationship exists between overexpression of Cripto-1 and

neurodegenerative disease. This would be unpredictable as the specification teaches a single study of 4 macaque infected with SHIV compared to a single control that was not infected. A single experiment with such a small size sample cannot be reasonably extrapolated to any mammals. First the Cripto-1 expression may be a result of the viral infection, exsanguinations, or handling of the sample as gene expression in general is variable and the specification teaches macaque are out bred models, suggesting greater variability in gene expression patterns. Second the art nor the specification suggests that macaque are a reasonable model for any mammal let alone humans.

Further there is no evidence in the specification or art that the neuroAIDS induced by the SHIV infection is representative of "any" neurodegenerative disease. The specification teaches a study of 5 macaque, 1 control and 4 infected. However, the specification and art do not teach or suggest that the macaque model of neuroAIDS is representative of Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and encephalitis. It would thus be unpredictable to associate overexpression of Cripto-1 in macaque infected with SHIV to any neurodegenerative disease or Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and encephalitis as the specification and art do not suggest or teach a nexus as to how neuroAIDS is representative of neurodegenerative disorders or the recited diseases.

Further the skilled artisan would have to determine what level of "overexpression" is required to result in a predictable association of Cripto-1 and neurodegenerative disease. This would be unpredictable as the specification teaches a single study with 1

control and 4 infected macaque. Cheung teaches that there is natural gene variation among individuals, thus the teachings of Cheung suggests the non-treated macaque may simply be an outlier. Further the specification and claims do not set forth what is required for Cripto-1 to be overexpressed, although the specification does teach an "arbitrary" 2.5 fold increase in expression. Thus the skilled artisan would have to determine what level of over expression is required to be correlated with neurodegenerative disease. This would further be unpredictable as the specification not claims teach what genes were used to normalize the expression data between samples and Vandesompele teaches normalization of data is critical and improper normalization can result in large errors in data and experimental interpretation. Finally the overexpression is unpredictable as Newton and Wu suggest that gene expression data is often skewed by the data selected and must be replicated, and the instant study doe not appear to have been in any model system.

Finally instant claims and specification do not set forth any nexus for the role of increased Cripto-1 mRNA or protein expression in neurodegenerative disease. The skilled artisan would thus have to determine if altered Cripto-1 expression is a correlated with the neurodegenerative disease, merely a result of the infection, tissue handling or normal variability of gene expression. As the specification and art set forth no mechanistic or hypothesized link as to the role of increased Cripto-1 mRNA or protein expression in neurodegenerative disease, the skilled artisan would have to determine if there is a casual relationship between Cripto-1 expression levels and neurodegenerative disease. In view of teachings of the art as to the variability of

expression data as a whole, the limited population studied, and the use of a single control, the skilled artisan would have to undertake unpredictable and undue trial and error experimentation to determine if such a relationship exists in mammals.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

5. Claims 1 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 1 and 15-20 encompass a method of detecting "any" Cripto-1 gene product in any mammal. The claims thus broadly encompass detection of mRNA or protein. Claim 17 draws the invention to humans, while claim 19 draw the invention to sequences identified by probes consisting essentially of SEQ ID NO 3 and SEQ ID NO 4. The claims do not set forth any structural requirements for a Cripto-1 gene product. The claims do not recite any particular conditions for using the oligonucleotide probes for RT-PCR and does not state how the probes are used for RT-PCR and therefore the claims encompass the detection of a large genus of nucleic acids that share any percentage of complementarity over any region with SEQ ID NO 3 and 4.

Claim 19 thus includes the detection of homologues, splice variants, allelic and mutant variants of SEQ ID No: 1.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches including, "any mammals, but not limited to, mammals of the order Rodentia, such as mice, the order Logomorpha, such as rabbits, the order Carnivora, including Felines (cats) and Canines (dogs), the order Artiodactyla, including Bovines (cows) and Swines (pigs), the order Perssodactyla, including Equines (horses), the order Primate's, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). An especially preferred mammal is the human." Thus the claims analyzed in light of the specification encompass at the Cripto-1 gene from at least 4,629 species (see Earthtrends.wri.org). This is an enormous genus of nucleic acids.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches the Cripto-1 gene is SEQ ID No 1, and Genbank accession M96955. The specification further teaches the amino acid sequence of Cripto-1 is SEQ ID NO 2. The specification does meet the written description requirement for a Cripto-1 nucleic acid consisting of SEQ ID NO 1 and a Cripto-1 protein consisting of SEQ ID NO 2. The specification does not set forth the sequence of Cripto-1 in any species other than human.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides the no limitations for the Cripto-1 gene. The claims read in light of the specification encompass any nucleic acid molecule that can be broadly called a Cripto-1 gene.

The art teaches there are 4629 species of mammals (see Earthtrends.wri.org). The art further teaches there are at least 46 known cDNA, 10 SNPs and 6 Cripto-1 pseudogenes in the 5 species in which Cripto-1 has been identified (see genecards.org/cgi-bin/cardisp.pl?gene=TDGF1&search=Cripto, pages 1-9, 11-5-2007). This is a large genus of nucleic acids that cannot reasonably be described by a single sequence. Further the claims broadly encompass at least 4500 plus other nucleic acid sequence that have not described, assuming a single Cripto-1 gene in each species. Thus the claims are drawn to an enormous genus of nucleic acids in which only a single species was possessed. The specification does not teach or suggest any specific features or functional attributes to identify other members of this broad genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid Cripto-1, do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of

the nucleic acids encompassed by the claimed nucleic acid. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding Cripto-1 is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules encompassed. The specification does meet the written description requirement for a Cripto-1 nucleic acid consisting of SEQ ID NO 1 and a Cripto-1 protein consisting of SEQ ID NO 2.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Summary

NO claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Carla Myers/
Primary Examiner, Art Unit 1634